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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,071	10/23/2002	Michael E. O'Donnell	22221/1023	1435

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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,071	O'DONNELL ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,36-38 and 55-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 36, 37, 38 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

1. Applicant's response filed on 12/7/05 is acknowledged.

Status of claims

2. Claims 2-35, 39-54 and 58-91 are canceled.

Claims 1, 37 and 38 have been amended.

Claims 1, 36, 37, 38 and 55-57 are pending and under examination.

Specification Informalities withdrawn

3. In view of amendment to the specification, the informalities have been withdrawn.

Claim Rejections - 35 USC 102 withdrawn

4. In view of amendment to the claim 1, the rejection under 35 U.S.C. 102(b) as being anticipated by Moriya et al 1985, Nucleic acids research, Vol, 13, 2251-2265 is withdrawn.

Claim Rejections - 35 USC 112, first paragraph maintained

5. The written description rejection of claims 1, 36-38 and 55-57 under 35 U.5.C. 112, first paragraph is maintained as set forth in the previous office action.

Claims are drawn to an isolated DNA molecule from a Gram positive bacterium selected from the group of *Staphylococcus, Streptococcus, Enterococcus, Mycoplasma, Mycobacterium, Borrelia, Treponema, Rickatsia, Chlamvdia, Helicobacter, and Thermatoga*, said isolated DNA molecule comprising a coding region from a dnaN gene wherein the coding region encodes a polypeptide that has activity as a beta clamp and is capable of functionally interacting with a polymerase during DNA polymerization and wherein the isolated DNA molecule hybridizes to the complement of SEO ID NO: 27 under conditions comprising a hybridization buffer comprising 0.9M SSC at 37^0C and washing in 0.2X SSC at 42^0C, said Gram positive bacterium is Streptococcus pyogenes, said amino acid sequence comprising the SEO ID NO:28, said the DNA molecule comprises the nucleotide sequence of SEO ID NO:27. Claims are also drawn to expression system comprising an expression vector into which the isolated DNA from S.pyogenes was inserted along with a heterologous DNA molecule and a host cell comprising said DNA and a heterologous DNA molecule.

The specification describes an isolated DNA sequence from *S.pyogenes* (group A, type 6, strain D471) comprising the nucleic acid sequence (1124 nucleic acids) SEQ.ID.NO: 27 and is named as dnaN gene. The specification on page 17 teaches that this gene encodes beta sub unit of

DNA polymerase comprising the amino acid sequence, SEQ.ID.NO: 28 having 378 amino acids. However, the specification does not disclose an isolated DNA molecule from other gram-positive bacteria as claimed. Further, the function of this gene (i.e., SEQ.ID.NO: 27) or its product (SEQ.ID.NO: 28) in assessing *S.pyogenes* infection or pathogenesis has not yet been identified. The specification fails to disclose the structure of an isolated DNA molecule comprising a coding region from dnaN gene from all *Streptococcus* spp such as *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus equismilis, Streptococcus bovis, Streptococcus anginosus Streptococcus pneumoniae Streptococcus mutans Streptococcus salivarius Streptococcus sanguis* Streptococcus *mitis* Streptococcus milleri *or* Staphylococcus spp such as Staphylococcus aureus (coagulase-positive) Staphylococcus epidermidis(coagulase-negative) , Staphylococcus saprophyticus (coagulase-negative),. Similarly none of the isolated DNA from Enterococcus, Mycobacterium, Treponema. Rickatsia have been discloses. However, Chlamydia, Mycoplasma, Borrelia. Helicobacter, Treponema appears to belong to gram-negative bacteria. Therefore, none of the isolated DNA meet the guidelines on written description. None of the above polypeptides meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116). The specification fails to teach the structure or relevant identifying characteristics sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Applicant's arguments filed on 9/10/05 have been fully considered but they are not deemed to be persuasive.

Applicant states that the specification teaches the relatedness of the homologs from other Gram-positive bacteria (shown in Figure 20E) demonstrating that the applicants were in possession of the claimed invention. The Examples further support the recited beta clamp activity, where it is shown that *S. aureus* interacts with both *S. aureus* and E. coli (a Gram negative) polymerases on linear DNA s (Example 9 and Figure 5A), *S. aureus* polymerase on circular DNA (see Example 10 and Figure 5B), and *S. pyogenes* β interacts with *S. pyogenes* polymerase (Examples 31, 34, and 35).

The examiner disagrees with the applicant because the disclosure does not teach isolated DNA molecule comprising coding region of dnaN from all *Streptococcus* spp such as *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus equismilis, Streptococcus bovis, Streptococcus anginosus Streptococcus pneumoniae Streptococcus mutans Streptococcus salivarius Streptococcus sanguis* Streptococcus *mitis* Streptococcus milleri , Staphylococcus epidermidis, *S.hominis etc Enterococcus, Mycoplasma, Mycobacterium, Borrelia, Treponema, Rickatsi etc.* In addition, *Chlamydia, Mycoplasma, Borrelia* and *Helicobacter* are not gram-positive bacteria as claimed but belong to gram-negative bacteria. The examiner looked at figure 20 E as directed by the applicant and noted that amino acid sequences of various bacteria have been retrieved from GenBank or individual unfinished genome databases (see page 23) and compared using computer program for homology analysis. Therefore, they are not isolated as the specification fails to provide support for the isolated DNA from all gram-positive bacteria. Further, page 23, line 29-32 discloses, "due to the low homology of delta one must "walk" from one organism to the next in order to recognize the homologue –". While dnaN from S.pyogenes may be interacting with polymerase but none of the examples indicate the function of this gene or its product in infection or disease or having anti-microbial activity. Additionally the beta clamp does not assemble onto DNA by itself and requires the assistance of y complex. Therefore, the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art had possession of the claimed invention.

6. The scope rejection of claims 1, 36-38 and 55-57 under 35 U.5.C. 112, first paragraph, is maintained as set forth in the previous office action.

The specification, while being enabling for an isolated DNA molecule from *Streptococcus pyogenes (S.pyogenes)* consisting of the nucleic acid sequence, SEQ.ID.NO: 27 encoding the amino acid sequence, SEQ. ID. NO: 28, an expression vector comprising said nucleic acid and a host cell comprising said expression vector does not reasonably provide enablement for "an

isolated DNA molecule from all gram positive bacteria ----at 42^{0}C ". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the disclosed invention is drawn to identifying new genes, involved in bacterial replication from the Gram-positive bacteria *Streptococcus pyogenes* (e.g., S. pyogenes). They are assigned names based on their nearest homology to subunits in *the E. coli* system. The genes encoding *E. coli* replication proteins are alpha (dnaE), epsilon (dnaQ), theta (holE), tau (full length dnaX), gamnma (frame shift product of dnaX), delta (holA), delta prime (holB), chi (holC), psi (holD), beta (dnaN), DnaB helicase (dnaB) and primase (dnaG). The state of the art indicates that each bacterium is structurally different and there is very little information available in replication mechanisms of Gram-positive organisms, Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes. The art indicates that three DNA polymerases I, II and III are involved in gram-negative bacterial replication. However, whether the S. pyogenes three component polymerase can synthesize DNA in as rapid and recessive fashion as the E. coli Pol III holoenzme three component polymerase is very difficult to predict, because no other DNA polymerase known to date catalyzes synthesis at the rate or processivity of the E. coli three component polymerase indicating the unpredictability in the art. Whether the claimed dnaN gene or its product involved in critical cell function, such that blocking its action with a drug causes the pathogenic cell to die or no longer proliferate in a screening assay for the identification of an anti-microbial drug utilizing a peptide encoded by an operon comprising a nucleotide sequence SEQ.ID.NO: 27 *S. pyogenes* is yet to be experimented. The specification on page 13 recite that the three component polymerase can synthesize DNA as rapid as the *E. coli* Pol III holoenzme three component polymerase is very difficult to predict. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for isolated DNA molecule from all other gram positive bacteria or gram positive bacteria that are going to be discovered, It is recognized in the art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). Therefore, based on the computer analysis of the amino acid sequence must be considered highly unpredictable, requiring a specific demonstration of efficacy on a case-by-case basis. The specification provides no disclosure how the product of dnaN may be used as a target for replication or potential drug screening because it fails to provide guidance whether this gene has the ability to interfere in replication either by itself or with DNA polymerases or inactivate or bind to the drug indicating its potential anti-microbial activity. Absent such demonstration, the invention would require undue experimentation to practice as claimed.

Applicant's arguments filed on 9/10/05 have been fully considered but they are not deemed to be persuasive.

With respect to enablement issue, applicant states that the claims are directed to isolated DNA molecules, not to methods of use. The invention can clearly be used in (1) ex vivo

polymerase reactions, (2) to identify new pharmaceutical agents that can disrupt interaction between the replication enzyme components and/or with DNA substrate and cites pages 77-83 of the specification for support of using the product in various methods.

The examiner understands that the specification contemplates various methods of using the product, dnaN from *S.pyogenes*. Therefore, the claims are enabled for an isolated DNA molecule from *Streptococcus pyogenes* (*S.pyogenes)* consisting of the nucleic acid sequence, SEQ.ID.NO: 27 encoding the amino acid sequence, SEQ. ID. NO: 28, an expression vector comprising said nucleic acid and a host cell comprising said expression vector. As discussed in the written description, the specification fails to disclose the claimed invention for other gram-positive bacteria. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC 102 maintained

7. The rejection of claim 1 under 35 U.S.C. 102(e) as being anticipated by Doucette-Stamm et al U.S.Patent 6,699,703 is maintained as set forth in the previous office action.

Doucette-Stamm et al disclose an isolated DNA, SEQ.ID.NO: 1744 dnaN gene from Streptococcus (gram positive, claims 1, 35 and 36) comprising dnaN coding region (see sequence alignment) from position 1, ATG to 1133 which is 71.1 % identical to SEQ.ID.NO: 27. Therefore, this nucleic acid hybridizes to the claimed DNA under conditions disclosed in the claim. Thus, the prior art reads on claim 1.

Applicant's arguments filed on 9/10/05 have been fully considered but they are not deemed to be persuasive.

Applicant states that as demonstrated by the accompanying Declaration of Michael E. O'Donnell under 37 CFR 1.131, the applicants had invented the presently claimed subject matter prior to July 2, 1997. In particular, applicants had isolated and cloned the *S.aureus* dnaN gene, and expressed the encoded beta protein prior to July 2, 1997. Based on the homology

between *S.aureus* and *S. pyogenes* and other Gram-positive bacteria as discussed above, possession of the *S. aureus* dnaN gene is sufficient to establish possession of the presently claimed genus prior to July 2, 1997.

The Declaration filed on 12/9/05 under 37 CFR 1.131 has been considered but is ineffective to overcome the Doucette-Stamm et al reference because the evidence submitted is insufficient to establish that applicant invented the claimed subject matter i.e., isolated DNA from all species and strains of *Staphylococcus, Streptococcus, Enterococcus, Mycoplasma, Mycobacterium, Borrelia, Treponema, Rickatsi, Chlamydia, Mycoplasma, Borrelia* and *Helicobacter* prior to July 2,1997.

Based on the homology between *S.aureus* and *S.pyogenes* applicant is not in possession of genus Staphylococcus or genus Streptococcus because *Staphylococcus, agalactiae*, *Streptococcus anginosus*, *Streptococcus equismilis, Streptococcus bovis, Streptococcus anginosus, Streptococcus pneumoniae*, Streptococcus *mutans*, Streptococcus *salivarius, Streptococcus sanguis,* Streptococcus *mitis,* Streptococcus *milleri* , *Staphylococcus epidermidis, S.hominis* are structurally different microorganisms (see written description rejection) and therefore, the isolated DNA is structurally distinct and different to one another. Therefore, the rejection of record is proper and maintained.

8. The rejection of claims 1 and 55-56 under 35 U.S.C. 102(e) as being anticipated by Ueyama e t al U.S.Patent 6,245,906 is maintained as set forth in the previous office action.

Ueyama et al disclose an isolated DNA, SEQ.ID.NO: 2 dnaN gene from S.pyogenes (gram positive) comprising dnaN coding region (see sequence alignment) from position 2324, ATG to 3200 which is 74.9% identical to SEQ.ID.NO: 27. Therefore, this nucleic acid hybridizes to the claimed DNA under conditions disclosed in the claim. The prior art discloses that clinical isolate of Streptococcus pyogenes was cultured and genomic DNA was extracted. The extracted DNA was completely digested with restriction enzyme HindIII, then random cloned into vector pGEM-3Z and thus the limitations of claims 55-56 were anticipated by the prior art.

Applicant's arguments filed on 9/10/05 have been fully considered but they are not deemed to be persuasive.

Applicant states that Ueyama's apparent 102(e) date is January 1, 2000. Therefore, it is not a prior art.

The examiner disagrees with the applicant because Ueyama 's effective filing date of the application 09/381862 (Patent Number: 6245906) was not 1/11/2000 as stated by applicant. This application was a national stage entry of PCT/JP98/01288 International Filing Date: 03/23/1998 (issued as WO 9842845 A1 October 1, 1998) which claims priority to JP-0071077, March 25, 1997). Therefore, the prior art rejection is proper, considering the 102(e) as of the 3/25/1997. Therefore, this rejection is maintained.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 36-38 and 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as being vague for the recitation of "wherein an isolated DNA molecule ---the complement of SEQ.ID.NO: 27—" because it is not clear how an isolated DNA molecule from all gram positive bacteria comprising a coding region from dnaN gene encodes a polypeptide that has activity as a beta clamp would hybridize to the complement of SEQ.ID.NO: 27?

Claim 1 is also rejected as being vague for the recitation of "activity as a beta clamp" as it is not clear what is this activity?

Claims 36 is objected to because of the following informalities:

Claim 36 is objected as it depends on a canceled claim 35. Appropriate correction is required.

Remarks

11. No claims are allowed.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP ' 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number for submission of before-final amendments is (703) 872-9306. The Right Fax number for submission of after-final amendments is (703) 872-9307.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.